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(54) Title: SYNDECAN STIMULATION OF CELLULAR DIFFERENTIATION

(57) Abstract

Methods are provided for altering levels of syndecan within a cell. The methods include enhancing syndecan expression via administration of growth factors, preventing suppression of syndecan expression via administration of anti-steroid agents, and altering syndecan biochemistry within the cell. The methods are used to induce or maintain cellular differentiation, and to decrease the growth of malignant cells. Application of the methods to the treatment of patients, including humans, is provided.

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SYNDECAN STIMULATION OF CELLULAR DIFFERENTIATION

FIELD OF THE INVENTION

This invention is in the field of cancer biology and therapy. Specifically, the invention is to a method for altering the differentiated state of a cell by altering syndecan expression. The method allows for the normalization of the growth rate and differentiation state of malignant cells, such method being based on the stimulation of syndecan expression in malignant cancer cells. Re-expression of syndecan in such malignant cells promotes their normal differentiated phenotype and prevents their tumor formation. This method may also be applied to normal cells to increase their differentiation, and therefore support the maintenance of cells, e.g. keratin production to prevent baldness.

BACKGROUND OF THE INVENTION

It is becoming more evident that cell surface proteoglycans play an important role in the regulation of cell behavior (Ruoslahti *et al.*, *Cell 64*:867-869 (1991)). Through their covalently bound glycosaminoglycan side chains, such proteoglycans can bind various extracellular effector molecules (Jalkanen, *et al.*, in *Receptors for Extracellular Matrix*, J. MacDonald & R. Mecham, Editors, Academic Press, San Diego, pp. 1-37 (1991)). One central challenge in proteoglycan biology is the need to understand what directive a cell receives by binding different effector molecules via the cell surface proteoglycans. It is further imperative to investigate what kind of intracellular response such binding activates, thereby leading to altered behavior of the cell. The way to approach these questions is to create biological models which are dependent on the expression of any given proteoglycans.

Syndecan is the best characterized cell surface proteoglycan (Saunders *et al.*, *J. Cell Biol. 108*:1547-1556 (1989); Mali *et al.*, *J. Biol. Chem. 265*:6884-6889 (1990)). It was originally isolated from mouse mammary epithelial (NMuMG) cells as a hybrid proteoglycan containing both heparin sulfate and chondroitin sulfate glycosaminoglycan side chains (Rapraeger *et al.*, *J. Biol. Chem. 260*:11046-11052 (1985)). Recent studies have revealed its expression, not only on epithelial cells but also on differentiating fibroblasts of developing tooth (Thesleff *et al.*, *Dev. Biol. 129*:565-572 (1988); Vainio *et al.*, *J. Cell Biol.*

108:1945-1964 (1989)), on endothelial cells of sprouting capillaries (Elenius *et al., J. Cell Biol. 114*:585-596 (1991)) and on the surface of lymphocyte subpopulations (Sanderson *et al., Cell Regul. 1*:27-35 (1989)) intimating that its function can vary on the surfaces of different cells. Syndecan belongs to a family of proteoglycans with conserved plasma membrane and cytoplasmic domains but with dissimilar ectodomains (Mali *et al., J. Biol. Chem. 265*:6884-6889 (1990)). The conserved structure of syndecan suggests that it could participate in signal transduction through the plasma membrane.

Syndecan binds several extracellular effector molecules but this binding is selective. For example, syndecan binds interstitial collagens and fibronectin but does not bind to vitronectin or laminin (Koda *et al., J. Biol. Chem. 260*:8156-8162 (1985)); Saunders *et al., J. Cell Biol. 106*:423-430 (1988); Elenius *et al., J. Biol. Chem. 265*:17837-17843 (1990)). Moreover, syndecan isolated from tooth mesenchyme has revealed selective binding to tenascin not observed for syndecan from NMuMG cells (Salmivirta *et al., J. Biol. Chem. 266*:7733-7739 (1991)). This suggests variation in syndecan glycosylation that results in the selective binding properties for syndecan. Polymorphism of syndecan glycosylation has also been observed between simple and stratified epithelia (Sanderson *et al., Proc. Natl. Acad. Sci. USA 85*:9562-9566 (1988)); but whether these changes also reflect altered ligand recognition by syndecan remains unknown. Syndecan also binds growth factors, such as basic fibroblast growth factor (bFGF) (Kiefer *et al., Proc. Natl. Acad. Sci. USA 87*:6985-6989 (1990); Elenius *et al., J. Biol. Chem. 267*:6435-6441 (1992)). Very recently, Yayon and coworkers (Yayon *et al., Cell 64*:841-848 (1991)) and Rapraeger and co-workers (Rapraeger *et al., Science 252*:1705-1708 (1991)) have shown that heparin-like molecules are required for the binding of bFGF to its high affinity receptor, indicating that syndecan-like molecules can also modulate the growth factor response. The fact that cell surface proteoglycans can bind both growth factors and matrix components could theoretically imply a role in regulating, both temporally (timing of expression) and spatially (precise localization), growth promotion by immobilizing these effector molecules to the vicinity of cell-matrix interactions. This is supported by the intriguing pattern of syndecan expression in the development that follows morphogenetic rather than histological patterns (Thesleff *et al., Dev. Biol. 129*:565-572 (1988); Vainio *et al., J. Cell Biol. 108*:1945-1954 (1989) and Vainio *et al., Dev. Biol. 134*:382-391 (1989)), and moreover, that syndecan expression is localized to sites of active proliferation (Elenius *et al., J. Cell Biol. 114*:585-596 (1991) and Vainio *et al., Dev. Biol. 147*:322-333 (1991)).

In simple epithelium, syndecan is polarized to baso-lateral surfaces where it co-localizes with actin rich cytofilaments (Rapraeger *et al., J. Cell Biol. 103*:3683-2696 (1986)). Upon rounding, syndecan is shed from the cell surface by proteolytic cleavage of the core protein at the cell surface, a process which separates the matrix binding ectodomain from the membrane domain (Jalkanen *et al., J. Cell Biol. 105*:3087-3096 (1987)). By this way, syndecan has been proposed to be involved in the maintenance of epithelial morphology. Mouse mammary tumor cells (S115), when steroid-induced to modulate their morphology from an epithelial to a more fibroblastic or fusiform phenotype, lose syndecan expression (Leppä *et al., Cell Regul. 2*:1-11 (1991)), as to several other cell types *in vivo* when they transform (Inki *et al., Am. J. Pathol. 139*:1333-1340 (1991); Inki *et al., Lab. Invest. 66*:314-323 (1992)), suggesting a general loss of syndecan expression during malignant transformation.

SUMMARY OF THE INVENTION

It is therefore an object of the subject invention to provide a method of altering the differentiated state of a host cell by altering syndecan expression in such cell.

It is a further object of the invention to provide a method to induce and regulate syndecan expression, especially in cells which exhibit a malignant phenotype, regardless of the origin of transformation.

It is a further object of the invention to provide a treatment for the reduction of tumor growth in a patient in need of such treatment, by administration of a composition to such patient, such composition comprising efficacious amounts of one or more agents that stimulate syndecan synthesis in the tumor cells of such patient.

It is a further object of the invention to provide the DNA sequence and localization of promoter, suppressor and enhancer elements for the syndecan gene.

It is a further object of the invention to provide a method for the enhancement of syndecan expression in a host cell, by enhancing syndecan gene transcription.

It is a further object of the invention to provide a method for the enhancement of syndecan expression in malignant cells, by preventing suppression of syndecan gene transcription.

It is a further object of the invention to provide a biochemical method for the inactivation of suppressors of syndecan gene expression in malignant cells.

It is a further object of the invention to provide a method for the stimulation of cellular differentiation by enhancing syndecan expression in both malignant and normal cells.

It is a further object of the invention to provide a method for the stimulation of cellular proliferation and differentiation, thus tissue regeneration, especially in processes such as wound healing, by enhancing syndecan expression.

Further features, objects and advantages of the present invention will become more fully apparent from a detailed consideration of the following description of the subject invention when taken together with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Figure 1 is a diagram of the assembly of mouse syndecan gene and its promoter region.

Figure 2. Figure 2 is the complete sequence of the mouse syndecan gene [SEQ ID Nos. :1: (DNA) and :2: (protein)] and its proximal promoter. Regulatory sites for the expression of syndecan may also exist on the first intron following the first exon (see Figure 1).

Figure 3. Figure 3 is a diagram of the assembly of mouse syndecan promoter region and the localization of the enhancer and suppressor elements together with restrictions sites for three different enzymes.

Figure 4. Figure 4 is the complete sequence of the mouse syndecan enhancer element [SEQ ID No. :3: (DNA)].located 8-10 kbs upstream from the transcription initiation site as indicated in figure3.

Figure 5. Figure 5A (panels A-D) is a photographic presentation of reduced growth ability of syndecan-transfected cells in soft agar. Panel A (wild-

type S115 cells) and B (control transfected cells) are pictures of the colonies that are formed in soft agar in the presence of testosterone, a feature typical for hormone-transformed cells. This growth ability was not observed with two independent syndecan-transfected cell clones (panels C and D), demonstrating how syndecan re-expression can overcome the effect of hormone-induced transformation. Figure 5B is a graphical presentation of how syndecan-transfected cells lose their ability to form tumors in nude mice. Wild-type or control transfected cells produce tumors in testosterone-administered nude mice while syndecan transfected cells revealed a very low tendency to produce tumors.

Figure 6 is a graphical representation of enhanced syndecan expression in 3T3 cells by simultaneously administered basic fibroblast growth factor (bFGF) and transforming growth factor beta (TGF-ß). This is an example of how syndecan expression can be enhanced as a result of growth factor action in normal cells during the differentiation process.

Figure 7 is a graphical representation of enhanced syndecan expression by MCF-7 cells exposed to the anti-estrogen toremifene. When exposed to estrogen, syndecan expression in MCF-7 cells was reduced and the cells transformed. Subsequent treatment with the anti-estrogen (toremifene) restored syndecan expression to levels close to that found in cells not exposed to estrogen and aided the cells in maintaining their normal growth behavior.

Figure 8 is a graphical presentation of how the suppressor element (see figure 3) is acitve in S115 cells treated with testosterone. Indicated stretches of promoter sequences were transfected in hormone-treated S115 cells and analysed for their transcription activity as described in Example VI. A dramatic drop was observed wiht suppressor construct as indicated in Figure 3, and it was more obvious in transformed S115 (a) cells than in 3T3 cells (b).

Figure 9 is a graphical presentation of how the enhancer element is active in growth hormone-treated 3T3 cells. Various stretches of promoter were transfected in 3T3 cells and analysed for their transcription activities. Fragment pXb6, which is the same as illustrated in Figure 3 as an enhancer, revealed more than ten fold stimulation in 3T3 cells exposed to growth factors bFGF and TGFß if compared to non-treated cells.

DEFINITIONS

In order to provide a clearer and more consistent understanding of the specification and claims, including the scope to be given such terms, the following definitions are provided.

"Enhancement" or "Stimulation" of Syndecan expression. By "enhancement" or "stimulation" of syndecan expression" is meant an effect of increasing the synthesis of syndecan, either by the induction or de-suppression (de-repression) of syndecan gene transcription and/or translation.

Cell growth. By "cell growth" is meant cell replication, both controlled and uncontrolled.

Malignant. By "malignant" is meant uncontrolled cell growth.

More Differentiated Phenotype. In stating that a cell has a "more differentiated phenotype" is meant that the cell possesses a phenotype usually possessed by a certain cell type more differentiated than the cell, which the cell was deficient in prior to enhancement of syndecan expression according to the invention. This phenotype may be defined by one or more phenotypic characteristics. For example, an epithelial cell is a more differentiated phenotype of a mesenchymal-like shape; therefore, the ability of the method of the invention to maintain cells in an epithelial cell morphology rather than a mesenchymal-like shape is a more differentiated phenotype within the meaning of the definition. Continuous syndecan expression is necessary for the maintenance of terminal differentiation of epithelial cells.

Syndecan expression is also linked to the normal differentiation of mesenchymal cells. However, only a transient increase in syndecan expression is needed for normal differentiation in mesenchymal cells. Therefore, contrary to epithelial cells, expression of syndecan is not needed for maintenance of terminal differentiation in mesenchymal cell. To induce differentiation of a suitable mesenchymal precursor cell population (such as a "condensing mesenchymal" cell population) to a fully differentiated mesenchymal cell, there is needed only a transient expression of syndecan expression. Therefore, a terminally differentiated mesenchymal cell is a "more differentiated phenotype" than a condensing mesenchymal cell.

Other useful phenotypes that are present in syndecan-deficient cells and not in cells expressing sufficient syndecan include fusiform shapes with long filopodial extensions with extensive under-and overlapping of these processes (so that the cells appear to have a defect in cell adhesion).

In another example, syndecan-deficient NMuMG cells continue to secrete milk fat globule antigen (and thus appear mammary-like) and continue to express cytokeratins (thus appear epithelial-like). However, their actin-containing cytoskeleton is disorganized and their expression of beta$_1$ integrins and E-cadherins at the cell surface is markedly reduced. Upon expression of sufficient syndecan, these phenotypes are corrected so that there is no reduction in cell surface integrins or E-cadherin and the cell has an epithelial morphology. Therefore, the amount of cell surface integrins or E-cadherin are useful markers of syndecan expression and may be used to monitor what amount of a drug is needed for efficacious results according to the method of the invention.

Efficacious Amount. An "efficacious amount" of an agent is an amount of such agent that is sufficient to bring about a desired result, especially upon administration to an animal or human.

Administration. The term "administration" is meant to include introduction of agents that induce syndecan expression into an animal or human by any appropriate means known to the medical art, including, but not limited to, injection, oral, enteral and parenteral (e.g., intravenous) administration.

Pharmaceutically Acceptable Salt. The term "pharmaceutically acceptable salt" is intended to include salts of the syndecan-inducing agents of the invention. Such salts can be formed from pharmaceutically acceptable acids or bases, such as, for example, acids such as sulfuric, hydrochloric, nitric, phosphoric, etc., or bases such as alkali or alkaline earth metal hydroxides, ammonium hydroxides, alkyl ammonium hydroxides, etc.

Pharmaceutically Acceptable Vehicle. The term "pharmaceutically acceptable vehicle" is intended to include solvents, carriers, diluents, and the like, which are utilized as additives to preparations of the syndecan-inducing agents of the invention so as to provide a carrier or adjuvant for the administration of such compounds.

Treatment. The term "treatment" or "treating" is intended to include the administration of compositions comprising efficacious amounts of syndecan-

inducing agents to a subject for purposes which may include prophylaxis, amelioration, prevention or cure of a medical disorder, including tumor growth, hair growth.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Briefly, in its broader aspects the present invention comprehends a method for maintaining a differentiated phenotype in a normal (non-malignant) cell that otherwise would suppress syndecan expression, by maintaining syndecan expression in such cell. The invention also comprehends a method for inducing a more differentiated phenotype in a malignant cell that lacks (or is deficient in) syndecan expression, by stimulating syndecan expression in such a cell. As used herein, if a cell is said to "lack" syndecan expression, it is meant to include cells that are either completely deficient in syndecan protein or produce insufficient syndecan levels to maintain or attain a desired differentiated phenotype.

The methods of the invention will not only prevent the progression (worsening) of a transformation state and tumor growth of cells, but can also be used to maintain differentiated cells in their differentiated state so that they continue to perform differentiated functions characteristic of such cells. Examples of differentiated functions of non-malignant cells include the secretion characteristics of a cell (that is, the secretion of specific proteins and/or other macromolecules) and hair formation by epidermal cells of skin. Thus, according to the invention, administration of agents capable of inducing syndecan expression in epidermal skin cells of the scalp will promote hair growth among bald (or balding) people.

The subject method may be accomplished in a variety of manners including biochemical, chemical or even molecular biological type methods. While the method is applicable to a variety of cancer (both malignant and non-malignant) and normal cells, it is particularly adaptable for treating malignant cells which have become transformed. This includes cells transformed due to hormonal influences of the body or environmental influences, such as chemicals or radiation exposure. Especially, the tumor type is a tumor characterized by loss of syndecan, for example, a glioma, myeloma, carcinoma, sarcoma, lymphoma, or adenoma.

Generally, any cell genetically capable of expressing syndecan can be a cell stimulated to express syndecan by the method of the invention. Syndecan-

is naturally expressed in a wide variety of epithelial cells in mature and embryonic tissues and by various embryonic mesenchymal tissues undergoing inductive interactions with epithelia. In addition, syndecan is naturally expressed on Leydig cells and on developing B-lymphocytes and a subpopulation of plasma cells.

Enhanced syndecan expression may be achieved by administration of compositions containing a biochemically, and/or chemically and/or molecular-biologically active component to an individual. Compositions may be administered orally, intravenously, subcutaneously or locally, or by any other method which will allow cells, normal or malignant, to be exposed to syndecan expression enhancing component.

By a "biochemically" or "chemically" active component is meant a component that alters the endogenous syndecan biochemistry or chemistry of the target cell without altering syndecan gene expression *per se*. For example, such alterations may include altering the half-life of syndecan protein or mRNA, so as to increase levels of syndecan protein in the cell, for example, by altering the external domain of the cell's endogenous syndecan, or the cell surface membrane properties in general, so as to retain higher levels of syndecan on the cell surface; and, altering the syndecan protein active site(s), so as to enhance the efficiency of the syndecan response.

By a "molecular-biologically" active component is meant a component that alters endogenous syndecan gene expression in a manner that allows for an increase in cellular syndecan, such as, for example, by stimulating transcription, preventing (or reducing) suppression of transcription, de-repression transcription, and generally increasing levels of mRNA and/or translation efficiency.

It is known that cellular transformation involves activation of some cell growth stimulating genes (like oncogenes) and inactivation of some other genes, which work to suppress cell growth. It has recently been shown that loss of syndecan expression is observed upon transformation of cells, and that this suppression is due to syndecan gene inactivation (Leppä *et al.*, *Cell Regul.* *2*:1-11 (1991); Inki *et al.*, *Am. J. Pathol.* 139:1333-1340 (1991); Inki *et al.*, *Lab. Invest.* *66*:314-323 (1992)). This was demonstrated in several biological models of various known carcinogenic systems (oncogenes, chemical carcinogens, UV-light, hormone-exposure, etc.). Therefore, syndecan gene suppression is implicated in the development of cellular transformation.

Further, according to the invention, all the manipulations of such cells which can induce syndecan expression in malignant cells, also induce these cells to obtain a more differentiated phenotype, and thus, subsequently reduce their potential tumorigenic behavior and metastasis.

In a preferred embodiment, the cell in which syndecan expression is stimulated is a cell that is steroid-responsive. Examples of such steroid-responsive cells include breast cells, endometrium cells and prostate cells, especially in the malignant state. In a highly preferred embodiment, the cell is responsive to estrogen and/or androgen.

Examples of other cell types that will respond to the treatment of the invention include malignant and non-malignant mesenchymal cells.

The regulatory elements of a given gene are commonly located upstream from (5' to) the transcription initiation site. Syndecan, however, has a very peculiar gene structure, in which the first and second exons are separated by a very large intron (Figure 1). This could mean that, in addition to the base sequences upstream from the transcription site, syndecan expression may also be susceptible to regulation by base sequences located between first and second exons (Figure 2), that is, in the first intron.

It has now surprisingly been found that the syndecan gene has a strong enhancer element located 8-10 kb upstream from the transcription initiation site. The sequence of this enhancer element has been identified and is given in Figure 4 [SEQ ID. No. 3].

Manipulation of the upstream region of the syndecan gene can block its inactivation during malignant transformation. For example, replacement of the region in front of first exon of the syndecan gene with the glucocorticoid-inducible elements of mouse mammary tumor virus (MMTV) not only blocks syndecan suppression during malignant transformation, but also inhibits the ability or potential of cells to transform and become tumorigenic (Figure 3). These findings suggest a very important role for syndecan in the maintenance of normal epithelial morphology (Leppä *et al., Proc. Natl. Acad. Sci. USA 89*:932-936 (1992)).

Cells destined to differentiate during organ formation or tissue regeneration also exhibit enhanced syndecan expression (Vainio *et al., Dev. Biol. 147*:322-333 (1991); Elenius *et al., J. Cell Biol. 114*:585-595 (1991)). The component(s) responsible for the regulation of syndecan expression (either

directly or indirectly) have not yet been identified. Growth factors are candidates for this role since they are known to be involved in the regulation of early development and cellular differentiation (Heath *et al., Curr. Opin. Cell Biol. 3*:935-938 (1991)). Involvement of growth factors is also supported indirectly by the fact that the expression of two embryonally important growth factors (TGF-ß and FGF) has been shown to coincide with syndecan within developing tooth (Vaahtokari *et al., Development 113*:985-994 (1991); Wilkinson *et al., Development 105*:131-136 (1989)).

Based on these findings the possible effect of growth factors on the expression of syndecan has been tested. It was shown that both bFGF and TGF-ß alone, but especially if administered in combination, enhance syndecan expression by 3T3 cells (Figure 4). This stimulation is close to the levels observed in syndecan-expressing epithelial cells (Elenius *et al., J. Biol. Chem. 267*:6435-6441 (1992)) prior to their malignization (Leppä *et al., Proc. Natl. Acad. Sci. USA 89*:932-936 (1992)). These findings suggest that growth factors, and their derived fragments and domains may prove to be valuable for the development of an active tool for the regulation of syndecan expression.

Preferably, for treatment of humans and animals, a drug is administered that results in the enhancement of syndecan expression to levels sufficient to facilitate cellular differentiation in the degenerative stages of tissues. Such drugs are herein termed "syndecan-inducing agents." Syndecan-inducing agents include the growth factors and their derivatives that retain growth-factor activity. Examples of such growth factors include bFGF, and TGF-ß, whether administered separately or together.

Even more preferred is a syndecan-inducing agent that has good tissue and cell penetration so that it could directly interfere with suppressor(s) of syndecan expression within cell nuclei. Such a syndecan-inducing agent is the known antitumor drug toremifene. When toremifene, known to have good plasma membrane penetration, is administered to the hormone-transformed epithelial cells with reduced syndecan expression, the cells reverse their lowered syndecan expression, and induce syndecan levels to those close to the level observed with normal, non-transformed cells (Figure 5). This demonstrates that syndecan-inducing agents useful in the methods of the invention are known and available and that such agents can specifically prevent cellular malignization by blocking suppression of syndecan expression. Another useful drug in this regard is tamoxifen.

Such syndecan-inducing agents may be administered using currently available preparations, or in any pharmaceutically acceptable vehicle. The route of administration may be any route that delivers efficacious levels of the drug to the desired active site, for example, by injection.

For parenteral administration, preparations containing one or more syndecan-inducing agents may be provided to the patient in need of such treatment in combination with pharmaceutically acceptable sterile aqueous or non-aqueous solvents, suspensions and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oil, fish oil, and injectable organic esters. Aqueous carriers include water, water-alcohol solutions, emulsions or suspensions, including saline and buffered medical parenteral vehicles including sodium chloride solution, Ringer's dextrose solution, dextrose plus sodium chloride solution, Ringer's solution containing lactose, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers, such as those based upon Ringer's dextrose and the like.

The syndecan-inducing agent of the invention can be employed in dosage forms such as tablets, capsules, powder packets, or liquid solutions for oral administration if the biological activity of the syndecan-inducing agent is not destroyed by the digestive process and if the characteristics of the compound allow it to be absorbed across the intestinal tissue.

The syndecan-inducing agents may also be administered by means of pumps, or in sustained-release form. The syndecan-inducing agents used in the method of invention may also be delivered to specific organs in high concentration by means of suitably inserted catheters, or by providing such molecules as a part of a chimeric molecule (or complex) which is designed to target specific organs.

Administration in a sustained-release form is more convenient for the patient when repeated injections for prolonged periods of time are indicated.

The composition containing the syndecan-inducing agent can be manufactured in a manner which is in itself know, for example, by means of conventional mixing, granulating, dragee-making, dissolving, lyophilizing or similar processes. The compositions of the present invention that provide the syndecan-inducing agent, in and of themselves, find utility in their ability to slow or prevent tumor growth or tumor reappearance. The syndecan-inducing

compositions of the invention utilize the body's own mechanisms for promoting differentiation of specific cell types to its maximum potential.

In intravenous dosage form, the compositions of the present invention have a sufficiently rapid onset of action to be useful in the acute management of tumor growth.

Additionally, a low potency version is useful in the management of disorders wherein a tumor has been effectively treated and the patient appears to be in remission, but it is desired to maintain sufficient levels of syndecan-inducing agents in the patient so as to assist the body in preventing a recurrence of the tumor.

Typical doses of toremifene or tamoxifen, and other such syndecan-inducing agents useful in the methods of the invention for treatment of humans or other animals are 20-600 mg daily, and preferably 20-60 mg daily.

The examples below are for illustrative purposes only and are not deemed to limit the scope of the invention.

EXAMPLE I

Reversal of hormone-induced transformation by exogenous syndecan expression.

As previously described (Leppä *et al., Cell Regulation 2*:1-11 (1991)), S115 mouse mammary tumor cells were routinely cultured in DMEM. For experimental studies involving hormone treatment, inactivated fetal calf serum (i-FCS) was replaced with 4% dextran charcoal-treated fetal calf serum (DCC-FCS), which eliminates endogenous steroids from serum), and used either with or without testosterone (10 nM) and with or without dexamethasone (10 nM or 1 μM). Cells were plated at a density of 10,000 cells/cm^2 and the medium was replenished every 3 days.

Plasmid pUC19-hsynpr7 containing human syndecan cDNA (Mali *et al., J. Biol. Chem. 265*:6884-6889 (1990)) was digested with *Nae*I restriction endonuclease, and the derived 336 bp long-fragment was separated in and eluted from low melting agarose gel. Plasmid pUC19-hsyn4 (Mali *et al., J. Biol. Chem. 265*:6884-6889 (1990)) was digested with *Nae*I and *Hind*II (polylinker site), and the plasmid-containing fragment starting from base 487 was isolated. The *Nae*I fragment from hsynpr7 was ligated to the pUC-hsyn *NaeI/Hind*II

digested vector. The orientation of insert was verified by restriction enzyme analysis and sequencing. The derived plasmid, containing the full coding region of human syndecan core protein, was named pUC19-hsynfull. This plasmid was further digested with *Bam*HI and *Sph*I (polylinker site). A fragment containing syndecan coding region bases 150-1461 was isolated and blunt-ended, using Klenow and T4 DNA polymerase. Finally, this fragment was ligated to *Sal*I-linearized and blunt-ended pMAMneo vector (Clontech; Palo Alto, CA), resulting in a chimeric gene containing RSV-MMTV-LTR promoter connected to human syndecan coding region and SV-40 polyadenylation signal. The orientation was confirmed by restriction enzyme digestions. The plasmid was named pMAMneo-hsyn.

For control transfections, a 642 bp long-*Hind*III/*Pvu*II fragment of human growth hormone gene (consisting of exons 4 and 5; Bornstein *et al., J. Biol. Chem. 263*:1603-1606 (1988)) was blunt-ended and cloned into the same pMAMneo vector, as described above. This control construct was named pMAMneo-hGH.

All plasmids were isolated using the CsCl density gradient method. Before transfections, plasmids were linearized with *Mlu*I, chloroform/phenol extracted and ethanol precipitated.

Transfections were performed using Lipofectin™ (BRL), according to manufacturer's instructions. After selection for two weeks (G418; 750 µg/ml, Sigma), surviving clones were isolated from growth plates using cloning cylinders. The expression of human syndecan or growth hormone (consisting of exons 4 and 5) mRNAs was then confirmed by RNA isolation and Northern blot analysis. Clones expressing high levels of transfected genes were selected for further studies and characterizations. These stock cells were routinely cultured in the presence of G418 (300 µg/ml).

For the measurement of exogenous syndecan expression total RNA was isolated from wild-type S115 cells and cells transfected with human syndecan or growth hormone genes. RNA was extracted using 4M guanidine isothiocyanate and CsCl pelleting, as earlier described by Chirgwin *et al., Biochemistry 18*:5294-5299 (1979)). RNA from normal mouse mammary NMuMG and normal human mammary HBL-100 cells was used for comparison. RNA aliquots of 15 µg were separated in 1% formaldehyde agarose-gel electrophoresis and transferred to GeneScreen Plus™ hybridization membrane (New England Nuclear). Blots were hybridized with multiprime (Amersham)

labeled inserts of either mouse (PM-4) (Saunders *et al.*, *J. Cell Biol.* *108*:1547-1556 (1989)) or human syndecan (pUC19-hsyn4 *Bam*HI 1.1 kb fragment) (Mali *et al.*, *J. Biol. Chem.* *265*:6884-6889 (1990)), or with human growth hormone exons 4 and 5 (hGH) (Leppä *et al.*, *Proc. Natl. Acad. Sci. USA* *89*:932-936 (1992)) cDNAs, using the high stringency conditions suggested by the manufacturer of the membrane (New England Nuclear). All techniques based on modern molecular biology are fully explained in the literature such as in the laboratory manual entitled *Current Protocols in Molecular Biology*.

Anchorage independent cell growth was measured in a soft agar colony assay. The six well-plates were first covered with an agar layer consisting of 2 ml DMEM, 0.5% agar and 4% DCC-FCS. The middle layer contained 10^4 cells in 0.5 ml DMEM supplemented with 0.33% agar and 4% DCC-FCS, with or without 10 nM testosterone. The uppermost layer, consisting of medium (2 ml), was added to prevent drying of the agarose gels. The plates were incubated at 37°C in 5% CO_2 for 12 days after which cultures were evaluated and photographed.

Tumorigenicity of S115 wild type cells, one hGH transfected control clone and two clones expressing human syndecan-1 was measured in nude mice. For this cells were cultured in DMEM containing 5% FCS and 10 nM testosterone. After four days in culture, cells were harvested with trypsin, washed, and 10^7 cells suspended in 0.2 ml of DMEM were injected subcutaneously into back of athymic male nude mice (balb-C). Silastic testosterone capsule, which is known to increase the growth rate of S115 cells (King *et al.*, *J. Steroid. Biochem.* *7*:869-873 (1976)) was simultaneously implanted. Nude mice were examined regularly for tumor development and the size of the palpable tumors measured at intervals.

EXAMPLE II

Growth factors enhance syndecan expression.

NMuMG mouse mammary epithelial cells and 3T3 (NIH) mouse fibroblasts were routinely cultured in bicarbonate-buffered Dulbecco's modified Eagle's medium (DMEM; GIBCO) containing 10% FCS (GIBCO) and antibiotics, as previously described (Elenius *et al.*, *J. Biol. Chem.* *265*:17837-17843 (1990)). For experiments, cells were plated at equal density on culture dishes (Nunc) and grown to 60 - 70% confluency. Twenty-four hours before supplementing growth factor(s) to the medium, fresh medium containing 2%

CMS-FCS (Vogel *et al., Proc. Natl. Acad. Sci. USA 75*:2810-2814 (1978)) was replaced. Equally treated cultures without growth factor addition served as negative controls. Porcine TGFß1 (R&D), recombinant human bFGF (Boehringer) and murine EGF (Sigma) were used in final concentrations of 2.5 ng/ml (100 pM), 10 ng/ml (570 pM) and 1.2 ng/ml (200 pM) respectively, in all experiments. For quantitation and isolation of cell surface syndecan, media were discarded at time points indicated in the text and the cell layers were washed twice with ice cold phosphate buffered saline (PBS). Cells were scraped with a rubber policeman into ice cold PBS supplemented with 0.5 mM EDTA and centrifuged. After subsequent washes by resuspension and centrifugation the cell numbers were measured by counting the nuclei with a Coulter Counter (Coulter Electronics).

For quantitation of syndecan intercalated into the cell membrane, syndecan ectodomain was released by incubating washed cells in 20 µg/ml bovine pancreatic trypsin (Type III; Sigma) in PBS for 10 min on ice bath. After incubation the cells were centrifuged, leaving the ectodomain in the supernatant (Rapraeger *et al., J. Biol. Chem. 260*:11046-11052 (1985)). Sample volumes equal to 400,000 or 200,000 cells for 3T3 or NMuMG cells, respectively, were loaded on cationic nylon membrane (Zeta-Probe; BioRad) in a minifold-slot apparatus (Schleicher and Schuell), as previously described (Jalkanen *et al., J. Cell Biol. 105*:3087-3096 (1987)). Nonspecific binding was blocked by incubating the membrane for one hour at room temperature in PBS containing 10% FCS. Syndecan attached to the membrane was detected with a monoclonal antibody against mouse syndecan core protein (mAB 281-2) (Jalkanen *et al., J. Cell Biol. 101*:976-984 (1985)) that was radioiodinated by chloramine-T oxidation method (Stähli *et al., Meth. Enzymol. 92*:242-253 (1983)). The membrane was incubated overnight at 4°C with ^{125}I-labeled 281-2 in PBS + 10% FCS (10,000 CPM/ml). After five washes with PBS the bound antibody was visualized by autoradiography.

The accumulation of syndecan ectodomain into the medium was estimated by taking samples corresponding to 1/50 (3T3 cells) or 1/100 (NMuMG cells) of the total volume of the remaining medium at selected time points. The samples were analyzed by loading them to nylon membrane as described above. The autoradiography signal was quantitated with a GelScan XL ultroscan densitometer (LKB) using GelScan XL 2400 software (LKB).

For syndecan purification, cells were radiolabeled for 24 hours in low sulfate DMEM ($MgCl_2$ substituted for $MgSO_4$; 2% CMS-FCS) with 100 µCi/ml

$^{35}SO_4$ (New England Nuclear) in the presence or absence of growth factor(s). Cell surface trypsin-releasable material was collected, as described above, and after dialysis against Tris-buffered saline (TBS), the sample was loaded onto a 281-2-Sepharose CL-4B immunoaffinity column (Jalkanen *et al., J. Cell Biol. 105*:3087-3096 (1987)). Bound material was eluted with 50 mM triethylamine (TEA) (pH 11.5) and the amount of radioactive PG in each fraction was analyzed using cetylpyridiumchloride-impregnated Whatman 3MM filter discs (Rapraeger *et al., J. Biol. Chem. 260*:11046-11052 (1985)). For interaction experiments, fractions containing most of the labeled PG were pooled and dialyzed against PBS.

To obtain unlabeled syndecan ectodomain for interaction assays (see below) the same procedure was used except that no radioactive sulfate was added to the culture medium and the syndecan containing fractions eluted from the immunoaffinity column were detected by immuno-dot assay using mAB 281-2. The estimation of the molar concentration of syndecan was based on the use of previously determined syndecan concentration by total amino acid analysis (Jalkanen *et al., J. Cell Biol. 106*:953-962 (1988)).

SDS-PAGE and Western Blot - For western blot experiments cells were cultured 24 hours with or without growth factor(s). Syndecan ectodomain containing material released from the cell surface by trypsin treatment was fractionated on SDS-PAGE gradient (2 -15%) gel (O'Farrel, *J. Biol. Chem. 250*:4007-4021 (1975)). After electrophoresis, samples were transferred onto Zeta-Probe membrane using electroblotting 2005 Transphor apparatus (LKB). The syndecan antigen on the filter was detected with radioiodinated mAB 281-2 and the filter was washed, as described above for slot blot analysis.

Northern Blot - RNA was isolated from 3T3 and NMuMG cells using 4 M guanidine isothiocyanate and CsCl density centrifugation (Chirgwin *et al., Biochemistry 18*:5294-5299 (1979)). RNA samples were size-separated on 1% agarose formaldehyde gel, transferred to GeneScreen Plus™ membrane (New England Nuclear) and hybridized with multi-prime (Amersham) labeled partial cDNA clone for mouse syndecan (PM-4) (Saunders *et al., J. Cell Biol. 108*:1547-1556 (1989)). After hybridization the membrane was washed in 2 x SSC and 1.0% SDS at 65°C (high stringency conditions). For rehybridization with glyceraldehyde-3-phosphate-dehydrogenase (GAPDH; Fort *et al., Nucleic Acid Res. 13*:1431-1442 (1985)) the bound PM-4 probe was removed as recommended by the manufacturer of the filter (NEN).

EXAMPLE III

Induction of syndecan mRNA expression in the human breast cancer cells (MCF-7) growth-inhibited with toremifene.

The steroid-responsive human breast cancer cell line MCF-7 was used to study the expression of human syndecan under different growth conditions regulated by estrogen and antiestrogen. For the experiment cells were plated at a density of 1.2×10^6 cells/100 mm ø plastic culture dishes and grown as monolayer cultures in 10 ml per dish of phenol red-free DMEM medium with 5% dextran/charcoal stripped fetal calf serum (DS-FCS), 2 mM L-glutamine and 3 µg/ml insulin. For hormone-treatment 1 nM 17ß-*O*-estradiol (E_2), alone or with 1-6.25 µM toremifene, dissolved 70% in ethanol, were added to the culture medium on the day following plating. The cells were cultured for 6 days, and the media were changed every second day. For RNA extraction the cells were washed *in situ* with PBS and scraped from the plates in 4 M guanidine isothiocyanate.

EXAMPLE IV

Treatment of Steroid-Responsive Tumors in Patients.

Patients diagnosed as having a steroid-responsive tumor selected from a breast tumor, an endometrium tumor, a prostate gland tumor or a mesenchymal tissue tumor are administered a composition that contains efficacious amounts of the anti-steroid agent toremifene or tamoxifen, or efficacious amounts of the growth factor bFGF, TGF-ß or bFGF together with TGF-ß, in amounts ranging from 20-600 mg per day, depending upon the extent of the tumor, the patient's age, the patient's sex, and other treatments such as are taken into consideration in designing such chemotherapeutic protocols. The syndecan-inducing agent is administered for a period of time sufficient to induce syndecan in the tumor cells, such that the tumor cells now take upon a more differentiated phenotype and such that the growth of the tumor is arrested or significantly slowed by the treatment.

EXAMPLE V

Stimulation of Hair Growth in Epidermal Skin Cells.

Patients diagnosed as being in need of increased hair growth in the scalp region are administered a composition that contains efficacious amounts

of the anti-steroid agent toremifene or tamoxifen, or efficacious amounts of the growth factor bFGF, TGF-ß or bFGF together with TGF-ß, in amounts ranging from 20-600 mg per day, depending upon the extent of the needed hair growth, the patient's age, the patient's sex, and other treatments such as are taken into consideration in designing such protocols. The syndecan-inducing agent is administered for a period of time sufficient to induce syndecan in the epidermal cells, such that hair growth is significantly increased by the treatment.

EXAMPLE VI

Dermination of Mouse Syndecan Promoter and Enhancer Activities

The mouse syndecan gene has been cloned and characterized up to -10 kbs upstream from the transcription start site. To determine the specific activities of different proximal promoter regions (up to -2 kbs from the start site) and enhancer regions (from -2 to -10 kbs) we have made plasmid constructs where these regions were cloned into pCAT basic or pCAT promoter vectors, containing the CAT reporter gene. The reporter CAT gene produces chloramphenicol acetyltransferase enzyme, which transfers the n-butyryl moiety of n-butyryl CoA to chloramphenicol. The n-butyryl chloramphenicol can be separated from native chloramphenicol by xylene.

For the further characterization of the proximal syndecan promoter a series of retriction enzyme treatments was made on the upstream region (Hind III, Hind II, Bgl II, Stu I, Dra I, Cla I, BamHI and Pst I -- Xho I) and the obtained fragments were cloned into the pCAT basic vector. For enhancer areas, three Xba I fragments were cloned into a pCAT promoter vector, where the SV 40 promoter was displaced by the Bgl II - Xho I fragment from the syndecan promoter.

The plasmid constructs were transiently transfected into eukaryotic cells by calcium phosphate precipitation simultaneously with a ß-Galactosidase expressing vector to determine the transfection efficiency. After a four hour incubation cells were treated with 15% glycerol and grown for approximately 48 h in cell culture medium. Cells were then scraped from dishes in TEN-buffer and the cytoplasmic extract was obtained by repeated freezing and thawing. ß-Galactosidase acitivity was obtained in hte cytoplasmic extreact by adding 0.1 M sodium phosphate, 45 mM mercaptoethanol and 0.2 mg ONPG. This was incubated from 2 hours to overnight and the colour reaction was measured spectrofotometrically at 420 nm.

The CAT activity was determined by adding 0.25 M Tris buffer, 25 ng n-butyryl CoA and 0.0626 μCi of ^{14}C-chloramphenicol to the cytoplasmic extract. These were incubated overnight, backextracted wiht xylene and radioactivity was measured by scintillation counting. The CAT activity was corrected for transfection efficiency by ß-galactosidase activity.

The cells used for proximal promoter constructs were 3T3 NIH, S115 (either hormone-treated of not) and nMuMG cells. For enhancer constructs we used 3T3 NIH cells grown in 2% CMS medium and to test the effect of growth factors in 2% CMS medium with 10 ng/ml FGF-2 and 2ng/ml TGFß-1.

All references cited herein are fully incorporated herein by reference. Having now fully described the invention, it will be understood by those with skill in the art that the scope may be performed within a wide and equivalent range of conditions, parameters and the like, without affecting the spirit or scope of the invention or any embodiment thereof.

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(ii) TITLE OF INVENTION: SYNDECAN STIMULATION OF CELLULAR DIFFERENTIATION

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(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)

(v) CURRENT APPLICATION DATA:
APPLICATION NUMBER: WO TO BE ASSIGNED
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(A) APPLICATION NUMBER: US 07/988427
(B) FILING DATE: 01-DEC-1992

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26700 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: join(4378..4443, 22026..22106, 23001..23483, 23905..24039, 24251..24418)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

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        160                 165                 170

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Val Leu Gly
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                                                         Gly Val

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(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 311 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

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(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2196 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

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WHAT IS CLAIMED IS:

1. A method of decreasing the growth of a malignant cell wherein said method comprises exposing said cell to efficacious levels of a compound that induces expression of syndecan in said cell.

2. The method of claim 1, wherein said induced expression is obtained by affecting the enhancer element of the syndecan gene (SEQ ID No. 3).

3. The method of claim 1, wherein said induced expression is obtained by affecting the suppressor element of the syndecan gene.

4. The method of claim 1,2 or 3, wherein said cell is steroid-responsive.

5. The method of claim 4, wherein said steroid is estrogen or androgen.

6. The method of claim 4, wherein said cell is selected from the group consisting of a malignant breast cell, an endometrium cell and a prostate cell.

7. The method of claim 6, wherein said method further comprises exposing said cell to an anti-steroid agent.

8. The method of claim 7, wherein said agent is toremifene or tamoxifen.

9. The method of claim 1,2 or 3, wherein said cell is a mesenchymal cell.

10. The method of claim 6 or claim 9, wherein said cell is a human cell.

11. The method of claim 1, wherein said cell is exposed to efficacious levels of a composition comprising growth factors of said cell.

12. The method of claim 11, wherein said growth factors are selected from the group consisting of bFGF; TGF-ß; and bFGF and TGF-ß.

13. A method for treating a patient in need of treatment to decrease the growth of a malignant tumor in said patient, wherein said method comprises administering, to said patient, efficacious levels of a composition that induces expression of syndecan in the cells of said tumor.

14. A method of claim 13, wherein said composition affects the enhancer element of the syndecan gene.

15. A method of claim 13, wherein said composition affects the suppressor element of the syndecan gene.

16. The method of claim 13, 14 or 15, wherein said tumor is a tumor whose growth is stimulated by steroids.

17. The method of claim 16, wherein said steroid is estrogen or androgen.

18. The method of claim 17, wherein said tumor is selected from a tumor the group consisting of a breast, endometrium, prostate gland or mesenchymal tissue.

19. The method of claim 13, wherein said composition comprises an anti-steroid agent.

20. The method of claim 19, wherein said agent is toremifene or tamoxifen.

21. The method of claim 13, wherein the efficacious agents in the composition comprise growth factors.

22. The method of claim 21, wherein said growth factor is selected from the group consisting of bFGF; TGF-ß; and bFGF and TGF-ß.

23. The method of claim 13, wherein said patient is a human.

24. A method of inducing differentiation of a cell to a more differentiated phenotype, wherein said method comprises exposing said cell to efficacious levels of a composition that induces expression of syndecan in said cell.

25. The method of claim 24, wherein the composition affects the enhancer element of the syndecan gene.

26. The method of claim 24, wherein the composition affects the suppressor element of the syndecan gene.

27. The method of claim 24, wherein the growth of said cell is stimulated by steroids.

28. The method of claim 27, wherein said steroid is estrogen or androgen.

29. The method of claim 24, wherein said cell is an epithelium cell.

30. The method of claim 29, wherein said epithelium cell is an epidermal skin cell.

31. The method of claim 24, wherein said cell is a human cell.

32. The method of claim 24, wherein said composition comprises an anti-steroid agent.

33. The method of claim 24, wherein the efficacious agent in said composition is toremifene or tamoxifen.

34. The method of claim 24, wherein the efficacious agent in said composition is a growth factor.

35. The method of claim 34, wherein said growth factor is selected from the group consisting of bFGF; TGF-ß; and bFGF and TGF-ß.

36. A method of stimulating hair growth in an epidermal cell of skin, wherein said method comprises stimulating expression of syndecan in said cell.

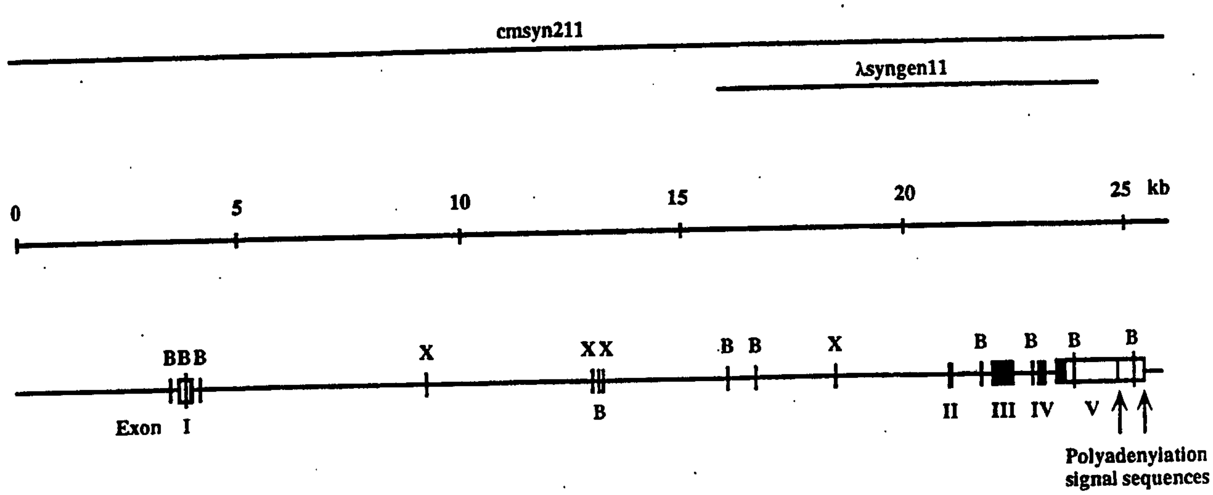
37. The method of claim 36, wherein said stimulated expression is achieved by affecting the enhancer element of the syndecan gene.

38. The method of claim 36, wherein said stimulated expression is achieved by affecting the suppressor element of the syndecan gene.

39. The method of claim 36, wherein said cell is a mesenchymal cell.

40. The method of claim 36, wherein said method comprises administering a composition comprising efficacious levels of a growth factor.

41. The method of claim 40, wherein said growth factor is selected from the group consisting of bFGF; TGF-ß; and bFGF and TGF-ß.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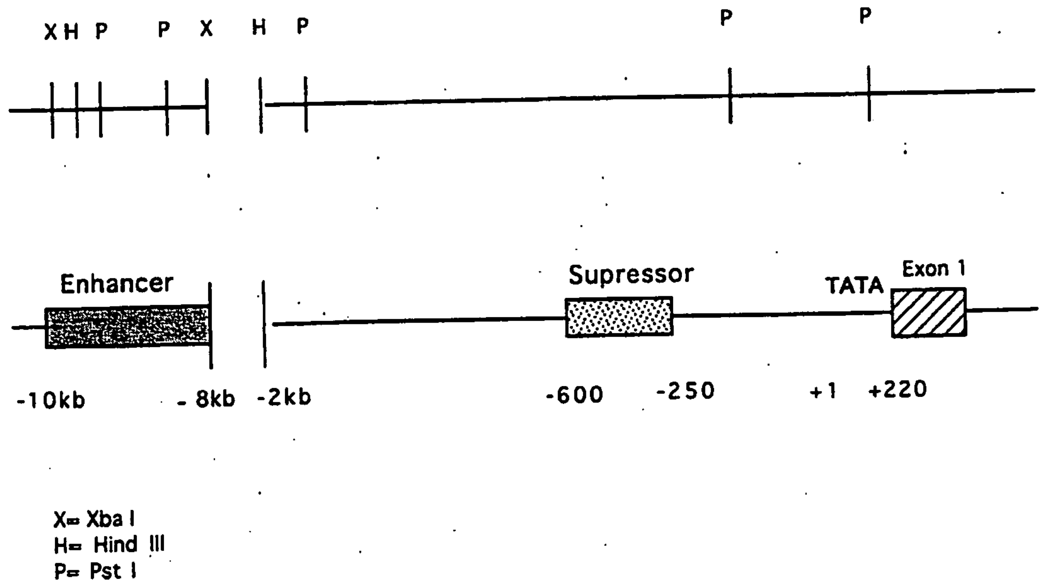
Polyadenylation
signal sequences

Fig 1.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P
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Supressor
TATA
Exon 1
-10kb
- 8kb
-2kb
-600
-250
+1
+220
X= Xba I
H= Hind III
P= Pst I

Fig 2.

Fig 3.

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Fig 4.

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TTGTGATTTA TGCCCCTGCT GGTGAGCCCA GGAATCCCTG TAGCACTCTC TCTCAGCTCT    960
AGGGCCCTGC TTGTGTATGG AAAACGCTTA GTGTTTTATA GGTATTTTGT CAGAATACTT   1020
TAAGGAACTT GACCAAAGTT ACAGGGAGGT TAGACAGATT GTCATGGTAT ACTCACCTCT   1080
GTCTCTGACC CTCCTAACTG GGACCTCTTT AGTCTCCCTT GAGGCAGGGA GTGCCACATG   1140
CATGTGTCCA GGCACATGTC TCCTGGTTTA CCTCCCAACG CACCTCAAGT CCCCAAGGTA   1200
GGTAGGCACT TGTATTCTGT AATTCAGAGA GGCAAATCAA ACTGTTACAA TGTTTGCCCA   1260
AAGCTCCCCA AGCAAAGTGG CCCTAAGAGT GAGCAAAGAG ACTGCGTGCC TTCACTGCCT   1320
GTGTGAATCC CTGCAGATAG TCTCTCATCT TGGTGCCCTT CCCACAGAGG CTGGGGCGGC   1380
AGGAGGGAGC CTGGACAGCT CAGACACTGG GTCATTGATG ACTGTTGTGT GGGATACCTG   1440
CCGGGGCGCA GGAGTGAGCC ATGCCACCCC AGGAAGTGGT TCAGGGTGAC TCTTCTTGGC   1500
ACACCTGGGA GGATGTAGCT GGTGCTGGCA CACCCACCGT CACGAGAGCT TCCTGTCCAA   1560
ACCTTCAACA AAGGCGGCTT CTTGAGACAG GCTAGACTGA AGTCACCAGC CTTGGGTGGG   1620
GTCCACTATG TAACCTCAGT GCTCAGGAAC CCTTTCCCAT ACTGTCTGGA ACTATACTGT   1680
ATGTAGCTGG GTTTCCACGC ATGTGTGCCT GCACCCAGTC CATCTCATCT TCTATCTCCC   1740
TCCCCTTTCC CGCTTCCCCC CTCCCCACTC TCCATCTCAT CTTCCATCCC CACCTCTTCT   1800
GGTCCCTGCC CTGCTAAACT CAGGGTAGCT GCATTCCGCT GGCCTTCCCC ATGTTCCAGG   1860
CTTCAGTCCC TTCTCTGCAC CTGTCCTTTG TGAAGTGACC AGAGGATTTC TGATCCTGTC   1920
TCTGTCGCTC TGAAGGGTCA GGAGTTCCTC CTGCCTGGAC AAAGCCATCC TGACGCACAT   1980
AAATAAAACA AACATCAAAC TCTATTCAAC CCCCTGGAAC CCGTGTGTGT TACTTACAGG   2040
GCAAAAGAAT GGAGCAGGGG ATGGGTTGTG GGGGGGGGGG GTGGCATCTG GGTTGTCTAC   2100
AGTTGTGCAT TAAGTTGTAA TTAAGATGTG CATTTCTCCA AATAAGGGAA AATTATTCTG   2160
GATTATTTGA GTGAAGCTGA AAGGTGATCA TCTAGA                             2196
```

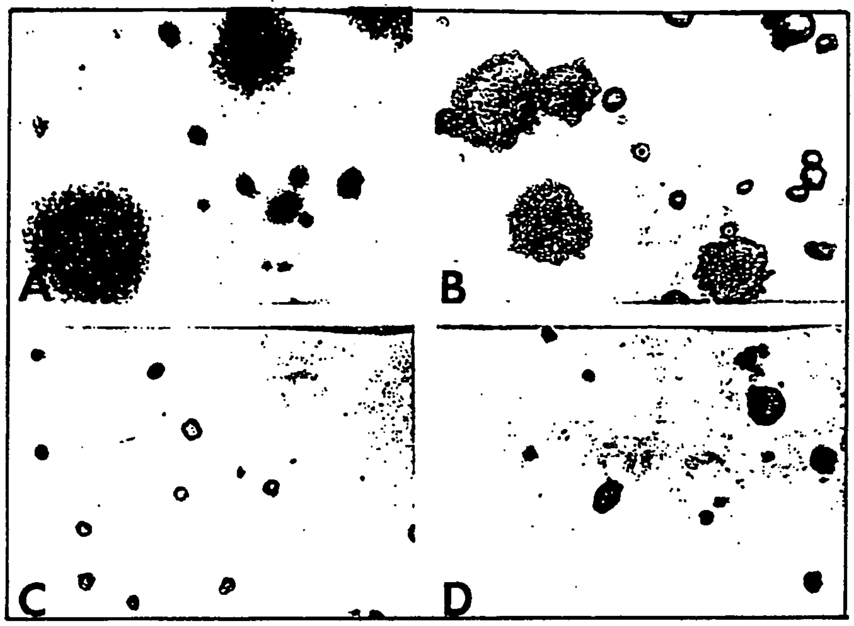

A
B
C
D

Fig 5A

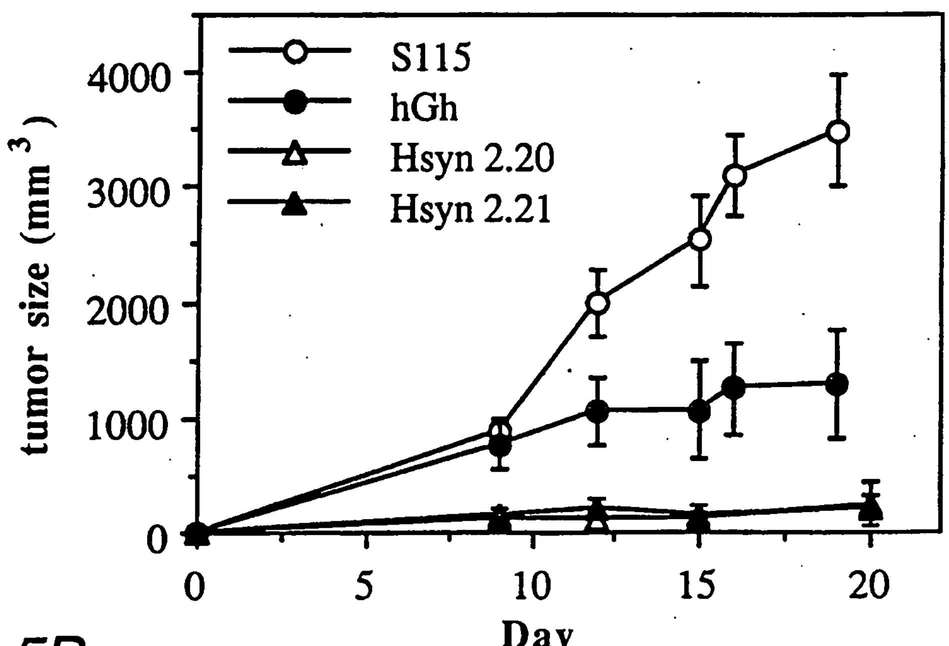

S115
hGh
Hsyn 2.20
Hsyn 2.21
4000
3000
2000
1000
0
tumor size (mm 3)
0
5
10
15
20
Day

Fig 5B

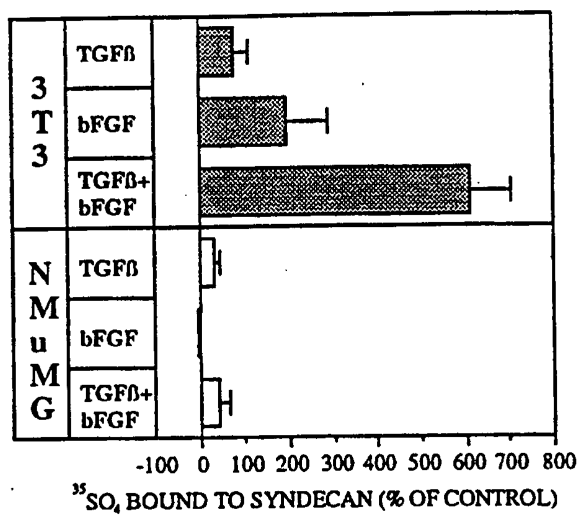

3T3
NMuMG
TGFß
bFGF
TGFß+ bFGF
-100 0 100 200 300 400 500 600 700 800
$^{35}SO_4$ BOUND TO SYNDECAN (% OF CONTROL)

Fig 6.

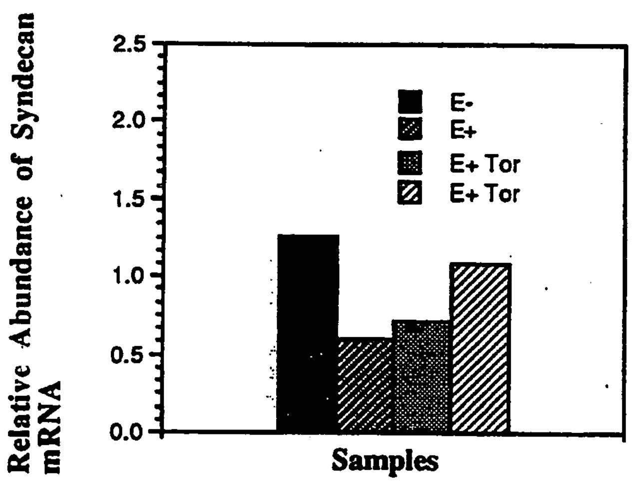
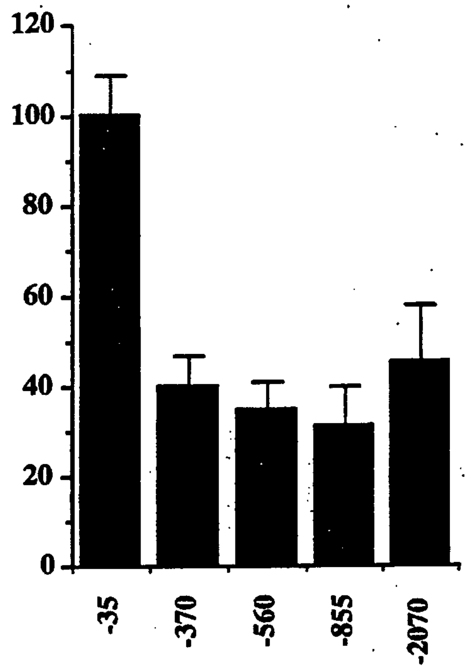

Relative Abundance of Syndecan mRNA
2.5
2.0
1.5
1.0
0.5
0.0
E-
E+
E+ Tor
E+ Tor
Samples

Fig 7.

a)


120
100
80
60
40
20
0
-35
-370
-560
-855
-2070

b)

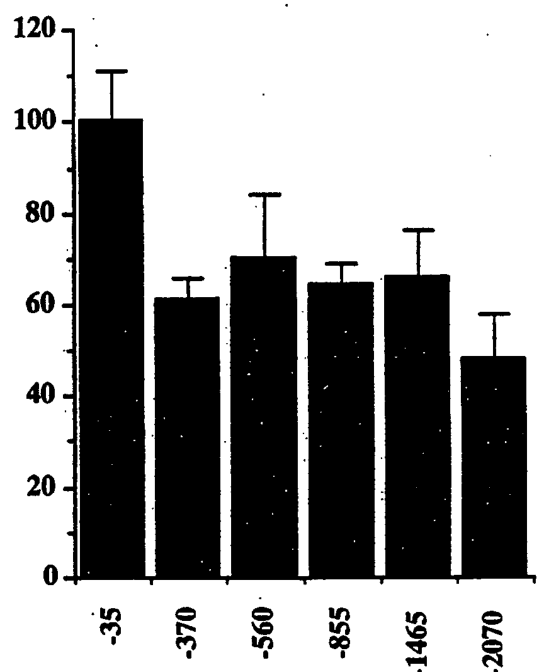

120
100
80
60
40
20
0
-35
-370
-560
-855
-1465
-2070

Fig 8.

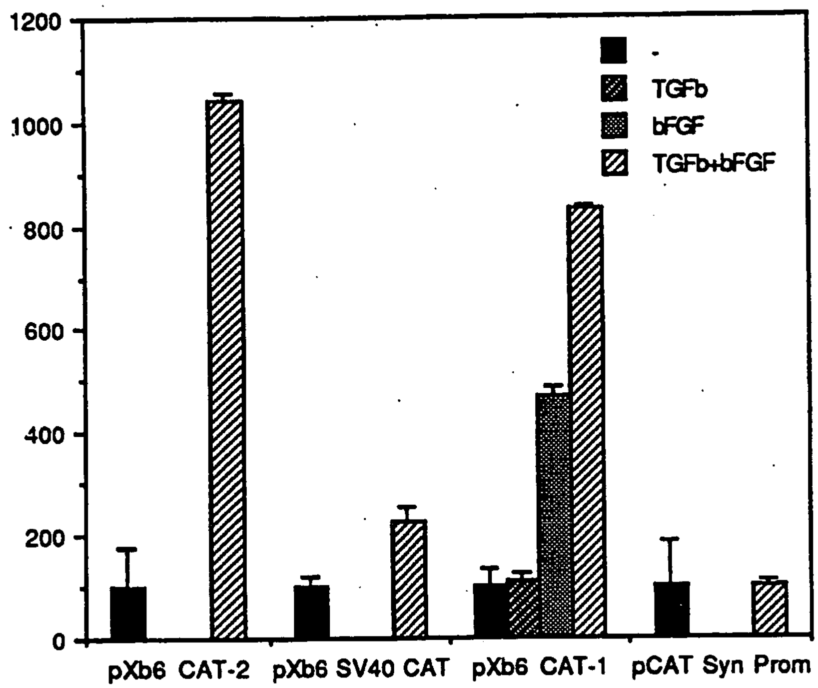

1200
1000
800
600
400
200
0
-
TGFb
bFGF
TGFb+bFGF
pXb6 CAT-2
pXb6 SV40 CAT
pXb6 CAT-1
pCAT Syn Prom

Fig 9.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[illegible]3/00514

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/135 A61K37/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CELL REGULATION vol. 2 , 1991 pages 1 - 11 S. LEPPA ET AL. 'STEROID-INDUCED EPITHELIAL-FIBROBLASTIC CONVERSION ASSOCIATED WITH SYNDECAN SUPPRESSION IN S115 MOUSE MAMMARY TUMOR CELLS' cited in the application see the whole document ---	1,3-7,9, 10,13, 15-19, 23,24, 26-32
Y	PROC. NATL. ACAD. SCI. vol. 89, no. 3 , February 1992 pages 932 - 936 S. LEPPA ET AL. 'SYNDECAN EXPRESSION REGULATES CELL MORPHOLOGY AND GROWTH OF MOUSE MAMMARY EPITHELIAL TUMOR CELLS' cited in the application see the whole document --- -/--	1-6, 9-18, 21-31, 34,35

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 March 1994	28.03.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P

International Application No
PCT/FI 93/00514

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BIOCHEMICAL SOCIETY TRANSACTIONS vol. 19, no. 4 , 1991 pages 1069 - 1072 M. JALKANEN ET AL. 'SYNDECAN, A REGULATOR OF CELL BEHAVIOUR, IS LOST IN MALIGNANT TRANSFORMATION' see the whole document ---	1-6, 9-18, 21-31, 34,35
Y	WO,A,92 13274 (JALKANEN) 6 August 1992 see abstract see page 7, line 15 - page 13, line 3 ---	1-6, 9-18, 21-31, 34,35
Y	JOURNAL OF CELLULAR BIOCHEMISTRY vol. SUPPL., no. 15F , 1991 page 223 M. JALKANEN ET AL. 'STIMULATION OF SYNDECAN GENE EXPRESSION IN MESENCHYMAL CELLS BY bFGF AND TGF-beta'	1-6, 9-18, 21-31, 34,35
A	see the whole document ---	36-41
Y	THE JOURNAL OF BIOLOGICAL CHEMISTRY vol. 267, no. 9 , March 1992 pages 6435 - 6441 K. ELENIUS ET AL. 'GROWTH FACTORS INDUCE 3T3 CELLS TO EXPRESS bFGF-BINDING SYNDECAN' cited in the application	1-6, 9-18, 21-31, 34,35
A	see the whole document ---	36-41
X	EP,A,0 335 554 (UNILEVER) 4 October 1989 see abstract see page 3, line 40 - page 5, line 26 see page 18, line 39 - page 19, line 40; claims; example 2 ---	36-41
X	EP,A,0 455 422 (MERCK & CO.) 6 November 1991 see abstract see page 7, line 12 - line 27; claims ---	36-41
A	THE JOURNAL OF CELL BIOLOGY vol. 114, no. 3 , 1991 pages 585 - 595 K. ELENIUS ET AL. 'INDUCED EXPRESSION OF SYNDECAN IN HEALING WOUNDS' see abstract see page 590 --- -/--	36-41

International Application No
PCT/[illegible]3/00514

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J.E.F. REYNOLDS 'MARTINDALE,THE EXTRA PHARMACOPOEIA' 1989 , THE PHARMACEUTICAL PRESS , LONDON see page 650 - page 651 see page 1625	1-23
A	EP,A,0 462 398 (HOFFMANN-LA ROCHE) 27 December 1991 see abstract see column 1, line 52 - column 2, line 12; claims; example 2	1-23
A	THE JOURNAL OF CLINICAL INVESTIGATION vol. 80, no. 5 , 1987 pages 1516 - 1520 L. SCHWEIGERER ET AL. 'BASIC FIBROBLAST GROWTH FACTOR AS A GROWTH INHIBITOR FOR CULTURED HUMAN TUMOR CELLS' see the whole document	1-23

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-41 are directed to a method of treatment of the human/ animal body the search has been carried out and based on the alleged effect s of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
please see attached sheet ../...

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

2. OBSCURITIES,...

A compound cannot be sufficiently characterised by its pharmacological profile on its mode of action as it is done by the expression like "compound that induces expression of syndecan". Therefore the search was limited to the compounds mentioned in the claims 8,12,20,22,33,35,41.

INCOMPLETE SEARCH:
CLAIMS SEARCHED COMPLETELY: 8; 12; 20; 22; 33; 35; 41
" INCOMPLETELY: 1-7; 9-11; 13-19; 21; 23-32; 34; 36-40

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inten al Application No
/FI 93/00514

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9213274	06-08-92	AU-A-	9071391	27-08-92
		EP-A-	0569367	18-11-93
EP-A-0335554	04-10-89	CA-A-	1325598	28-12-93
		JP-A-	1287013	17-11-89
		JP-C-	1770969	30-06-93
		JP-B-	4060567	28-09-92
		US-A-	5037643	06-08-91
EP-A-0455422	06-11-91	JP-A-	4224522	13-08-92
EP-A-0462398	27-12-91	US-A-	5147854	15-09-92
		AU-B-	636489	29-04-93
		AU-A-	7713991	12-12-91
		CA-A-	2042973	23-11-91
		JP-A-	5213772	24-08-93

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